Primary neuroendocrine carcinoma of the kidney

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Background. The objective of the study was to report a rare case of primary neuroendocrine carcinoma of the right kidney in a 36 year old male.

Methods. The patient was clinically assessed; CT and OctreoScan scintigraphy were performed and levels of 5-HIAA, vanillylmandelic acid and NSE were determined. The tumor and metastases were histologically and immunohistochemically examined.

Results. The imaging methods showed a cystic tumor in the lower pole of the right kidney. Macroscopically, the entire tumor was sized 8x8x7 cm. Histologically, it was made up of ribbon-line or trabecular patterns of tumor cells. Occasional adenomatoid and cystic structures were present. The tumor cell nuclei were round or oval, with no irregularities and fine lumpy chromatin. The mitotic count was < 1 /10HPF and the proliferation marker Ki-67 was < 1 % of tumor cells. Immunohistochemically, the tumor cells were positive with antibodies against chromogranin A, synaptophysin, CD56 (focally), cytokeratins AE1-AE3 (focally), vimentin (most cells), glucagon (focally), and pancreatic polypeptide (PP; focally). Antibodies against serotonin, somatostatin, gastrin, vasoactive intestinal polypeptide (VIP) and calcitonin did not react with the tumor. The results of biochemical markers (5-HIAA, vanillylmandelic acid and NSE) did not correlate with development or treatment of the tumor.

Conclusions. Primary neuroendocrine carcinoma of the kidney was diagnosed both histologically and immunohistochemically. The patient was clinically investigated using CT and OctreoScan scintigraphy. Within two years from nephrectomy, metastases were found in the right humerus and retrocaval lymph nodes. The metastatic lesions were surgically removed. Currently, the patient's condition is good, with no tumor progression detected.

Key words: kidney neoplasm, neuroendocrine tumor, carcinoid

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INTRODUCTION

Primary neuroendocrine tumors of the kidney are rare. They occur in both the renal parenchyma and the renal pelvis[1-6]. Individual tumors and series of five or six cases have been reported[7,8]. The largest series of 21 patients with renal carcinoids (well-differentiated neuroendocrine tumors) was investigated by Hansel et al.[6]. The patients were treated in five large US hospitals over a period of 36 years. So far, about 90 cases of the tumor have been described[9]. Most frequently, the tumor develops in the horseshoe kidney[10,11]. Hansel et al.[6] found the horseshoe kidney in 19% of cases. Sporadically, synchronous well-differentiated neuroendocrine tumors and adenocarcinoma within the teratoma of the horseshoe kidney have been reported[11].

CASE REPORT

A 36 year old male was admitted to the university hospital due to epigastric pain and dyspepsia three years previously. The 5-hydroxyindoleacetic acid (5-HIAA) test showed 41.0 μmol/24 hrs (reference range, 10.4-47.1 μmol/24 hrs). The vanillylmandelic acid level was 31.2 μmol/24 hrs (reference range, 0-33 μmol/24 hrs).

During the hospital stay, the vanillylmandelic acid levels fluctuated between 17.9 and 53.2 μmol/24 hrs. Serum neuron-specific enolase (NSE) levels did not exceed 10.3 μg/L (reference cut-off, 12.5 μg/L) throughout the hospitalization. Based on the clinical results, nephrectomy of the right kidney was performed.

Two months later, OctreoScan scintigraphy detected two lesions with increased somatostatin receptor density. One lesion was in the proximal third of the right humerus; the other was localized in the epigastrium but not specifically. The former lesion was assessed by CT angiography. Subsequent magnetic resonance imaging (MRI) confirmed a metastasis in the humerus but failed to show alterations in the epigastrium. One year later, a small increase in the right humerus lesion was revealed on X-ray. Subsequent biopsy examination confirmed metastatic neuroendocrine carcinoma. Two and half years after nephrectomy, resection of the humerus was performed. Postoperatively, PET/CT revealed a lesion in the retrocaval lymph nodes of the L1-L2 region. The nodes were surgically removed. Histological examination confirmed a neuroendocrine carcinoma metastasis. At present, the patient is free from tumor symptoms. His levels of the studied markers were of no value and no correlation with tumor development or treatment was found.

MATERIALS AND METHODS

The kidney and lymph nodes were fixed in neutral formalin and the tumor tissue specimens were processed in the Autotechnicon. The paraffin-embedded sections were stained with hematoxylin and eosin.

Immunohistological evaluation was carried out using the avidin-biotin complex (ABC) method as usual, according to the manufacturer's instructions. The following antibodies were used (dilutions as shown in the brackets): AE1-AE3, clone AE1-AE3 (1:50), CK20, clone Ks 20.8 (prediluted), CK7, clone OU-TL 12/13 (1:50), NSE, clone 2F11[1] (1:50), rabbit anti-human gastrin polyclonal antibody (1:2000), vimentin, clone Vim 3B4 (1:100), rabbit anti-human somatostatin polyclonal antibody, (1:1000), mouse anti-human serotonin monoclonal antibody, clone 5HT-H209 (1:100), rabbit anti-human glucagon polyclonal antibody, clone A0565 (1:1000) – the antibodies were produced by Dako, Glostrup, Denmark; synaptophysin, clone 27G12 (1:100), chromogranin A, clone 5H7 (1:100), CD56, clone 1B6 (1:50) – antibodies manufactured by Novocastra, Newcastle-upon-Tyne, UK; rabbit anti-pancreatic polypeptide polyclonal antibody, clone 18-0043 (1:100) – Invitrogen, Lofer, Austria; VIP (vasoactive intestinal peptide) (1:500) – Immunostar, USA; rabbit anti-calcitonin polyclonal antibody, clone SP17 (1:20) – Thermo Scientific, Fremont, USA.

RESULTS

Macroscopic findings

In the renal hilum, a 5x5x6 cm cyst was found. The cavity was filled with dark red liquid. The inner surface of the cavity contained brownish soft areas of tissue. The cyst cavity was just adjacent to compact whitish tumor nodules affecting the renal medulla. The overall size of the lesion was 8x8x7 cm (Fig. 1). The cyst was in the close proximity to the renal pelvis.

Histopathology

The tumor itself was made up of ribbon-like or trabecular patterns of cylindrical cells. The nuclei were round or oval, localized mostly in the cell center. Occasional pseudoglandular and cystic structures were present (Fig. 2). At the basal area of the tumor cells, the plasma was of granular appearance. The tumor cells had a mitotic count of <1mitosis/10HPF; the proliferation marker Ki-67 level was much lower than 1%. Metastases in the lymph node and humerus were of a histologically similar appearance to that in the kidney. Also in these places, the mitotic count was 1/10HPF and the Ki-67 index was 1-2%.

Immunohistologically, the tumor cells were positive with antibodies against chromogranin A (Fig. 3), synaptophysin (Fig. 4), CD56 (focally), vimentin (most cells), glucagon (focally), pancreatic polypeptide (PP) (focally), and cytokeratins AE1-AE3 (focally). The other markers were negative.

DISCUSSION

Well-differentiated neuroendocrine carcinoma is mostly observed in the gastrointestinal tract. Most frequently, it is localized in the small and large intestines and stomach. It is less frequent in the respiratory system. Sporadically, it is seen in parenchymal organs such as the liver and kidneys. In the liver parenchyma, it mostly arises from scattered neuroendocrine cells of bile duct or gall bladder mucosae. In the kidneys, the histogenetic origin of these tumors is unclear. The tumor quite often develops in the horseshoe kidney. In such cases, the clinical course is much more benign than in tumors occurring in normal kidneys[12].

Primary neuroendocrine carcinoma of the kidney is most prevalent in patients around 50 years of age. It is clinically manifested by hematuria and unspecified pain in the lumbar region. Shurtleff et al.[13] found that in approximately 20% (out of 43 cases), the course is asymptomatic. Gradually, the tumor enlarges and only then clinical symptoms may appear. In our case, it was 8 cm. In more than 48% of cases, the tumor is cystic, such as in our patient. In the aforementioned series of 43 patients with primary neuroendocrine carcinoma of the kidney, metastases in the lymph nodes were found in approximately 18%. Carcinoid syndrome was diagnosed in nearly 14% of cases. In the reported cases, tumor cells most frequently expressed PP, VIP and serotonin[12]. In our case, two years and six months after nephrectomy, lesions were found in the proximal humerus and lymph nodes paravertebrally in the subhepatic region. In both sites, metastases of well-differentiated neuroendocrine carcinoma were histologically confirmed. Expression of the proliferation marker Ki-67 was more prominent in these sites than in the primary tumor of the kidney.

The histogenetic origin of primary neuroendocrine carcinoma of the kidney is unclear. Neuroendocrine cells are not mentioned in histological descriptions of the normal parenchyma of the kidney, renal pelvis or ureter. Progenitor cells incorporated into the renal parenchyma during organogenesis are considered. Some authors[14,15] found small nests of paraganglionic cells from which neuroendocrine tumors may arise. Nests of these cells were detected in the hilar region of the kidney.

Parada et al.[16] reported chromophobe renal cell carcinoma with neuroendocrine differentiation, an entity described in the only case. According to the authors, both types of lesions have a common origin in renal tubular cells. Neuroendocrine differentiation was suggested by not only immunohistochemical assay but also neurosecretory granules found in tumor cell cytoplasm by electron microscopy. Rarely, neuroendocrine differentiation is observed in microcystic urothelial cell carcinoma of the renal pelvis[17]. Primary neuroendocrine carcinoma of the kidney may be mimicked by neuroendocrine cancer metastasis as reported in Merkel cell carcinoma metastatic to the kidney[18].

Some authors think that the tumors arise from neuroendocrine cells occurring in the mucosa of the renal pelvis in intestinal metaplasia[19,20].

Fig. 1. Section of the kidney with cystic tumor.

Fig. 2. Cylindrical cells of well-differentiated neuroendocrine carcinoma (HE, 400x).

The histological picture of the neuroendocrine carcinoma of the kidney was medium-sized tumor cells arranged into trabecules or ribbons. That is, structures similar to those observed in these tumors in the gastrointestinal tract. In our case, glandular structures were also seen that tended to form cyst cavities. One such cavity occupied a considerable part of the tumor. Less frequently, large cell neuroendocrine carcinoma is seen[21,22]. Some authors[23,24] claim that neuroendocrine carcinoma of the renal pelvis is more frequently associated with transitional cell carcinoma, adenocarcinoma or squamous cell carcinoma than with the same tumors arising in the renal parenchyma.
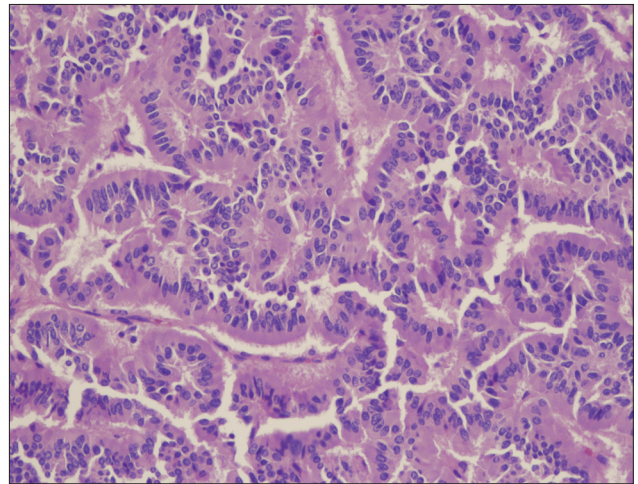
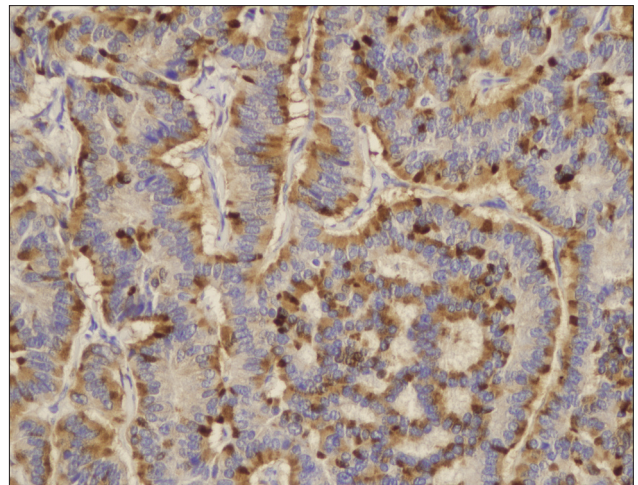At the molecular genetic level, abnormalities of chromosome 3 were detected[1].

Fig. 3. Tumor cells mostly at the basal area react positively with an antibody against chromogranin (400x).
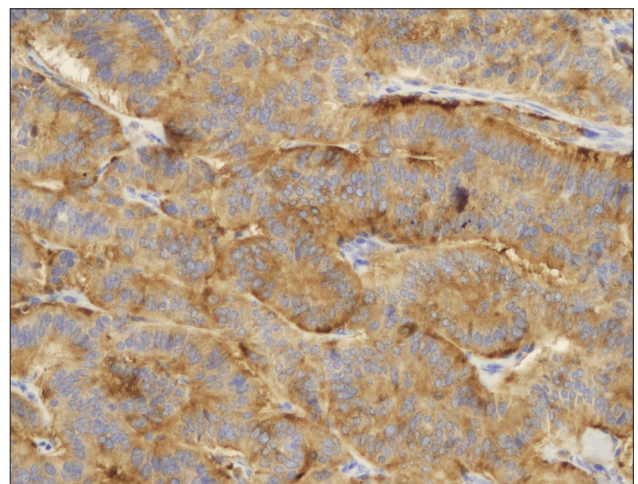
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Fig. 4. Positive finding in tumor cells with an antibody against synaptophysin (200x).

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